IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	
Istvan Szelenyi et al.	Group Art Unit: 1617
Application No.: 10/089,449	Examiner: SHOBHA KANTAMNENI
Filed: June 28, 2002	
For: NOVEL COMBINATION OF LOTEPREDNOL B2-ADRENOCEPTOR AGONISTS	

APPEAL BRIEF

Mail Stop APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This appeal is based on the decision by the Primary Examiner dated April 30, 2007 issuing a final rejection of Claims 1-4, 7, and 8, a copy presented in Claims Appendix of this brief.

☐ A check covering the ☐ $ 255 ☐ $ 510 Government fee is filed herewith.

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The Commissioner is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

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Table of Contents

I. Real Party in Interest 2
II. Related Appeals and Interferences 2
III. Status of Claims 2
IV. Status of Amendments 2
V. Summary Claimed Subject Matter 2
VI. Grounds for Rejections under Review on Appeal 4
VII. Arguments 5
VIII. Claims Appendix 20
IX. Conclusion 21

I. Real Party in Interest

MEDA Pharma GmbH & Co. KG is the real party in interest, and is the assignee of Application No. 10/089,449.

II. Related Appeals and Interferences

The Appellants' legal representative, or the assignee, does not know of any other appeal or interferences which will affect, or be directly affected by, or have bearing on the Board's decision in the pending appeal.

III. Status of Claims

Claims 1-4, 7, and 8 are pending in the present application, and are being appealed. Claims 5-6 have been cancelled.

IV. Status of Amendments

Claim amendments were not entered subsequent to the Final Office Action, dated April 30, 2007. In response to the Final Office Action issued on April 30, 2007, a reply had been filed on August 30, 2007, presenting amendments to all pending claims. An Advisory Action, issued on September 17, 2007, indicating that claim amendments filed in the reply of August 30, 2007 have not been entered for allegedly raising new issues that would require further consideration and/or search.

V. Summary of Claimed Subject Matter

Claims 1-4 are directed to powdered pharmaceutical compositions. Claim 7 is directed to a method for treating asthma bronchiale in a patient. Claim 8 is directed

to a process for preparing a pharmaceutical composition for the treatment of asthma bronchiale. Claims 1, 7, and 8 are independent claims.

Claim 1 recites, *inter alia,* a powdered pharmaceutical composition, comprising: an efficacious amount of (i) loteprednol or loteprednol etabonate; and (ii) at least one β_2 adrenoreceptor agonist selected from the group consisting of salbutamol, reproterol, salmeterol, formoterol, and pharmaceutically tolerable salts ... wherein the pharmaceutical composition is formulated in a powdered form. Support for powdered pharmaceutical compositions of Claims 1-4 is found throughout the specification, including at page 1, lines 4-13; page 3, lines 5-12 and 14-18; page 4, lines 11-15 and lines 17-19; Table 1 at page 5; Table 2 at page 6; Table 3 at page 8; and Examples 5-8 at pages 12-13.

Claim 7 recites, *inter alia,* a method for the treatment of asthma bronchiale in a patient, the method comprising: administering to the patient an efficacious amount of (i) loteprednol or loteprednol etabonate and (ii) at least one β_2 adrenoceptor agonist selected from the group consisting of salbutamol, reproterol, salmeterol, formoterol, and pharmaceutically tolerable salts there of, wherein a pharmaceutically acceptable excipient or a vehicle is added if suitable for simultaneous, sequential or separate administration. Support for the treatment of asthma bronchiale in a patient is found throughout the specification, including at page 4, lines 28-37; pages 10-11; Table 1 at page 5; Table 2 at page 6; Table 3 at page 8; and Examples 5-8 at pages 12-13.

Claim 8 recites, *inter alia,* a process for the preparation of a pharmaceutical composition for the treatment of asthma bronchiale, the process comprising: combining (i) an effective amount of the active compound loteprednol or loteprednol

etabonate and (ii) an effective amount of at least one β_2 adrenoceptor agonist selected from the group consisting of salbutamol, reproterol, salmeterol, formoterol, and pharmaceutically tolerable salts there of, wherein the composition thus obtained is converted into a powdered form suitable for inhalations. Support for the process to prepare a pharmaceutical composition is found throughout the specification, including at page 4, lines 28-37; pages 10-11; Table 1 at page 5; Table 2 at page 6; Table 3 at page 8; and Examples 5-8 at pages 12-13.

VI. Grounds for Rejections under Review on Appeal

A. Claims 1-4 and 8

Claims 1-4, and 8 stand rejected under 35 U.S.C. §103(a) as being unpatentable over *Keller et al.* ("*Keller*") (WO 9834595, English equivalent to US 6,461,591, PTO-892 of record), in view of *Palmer Douglas* ("*Palmer Douglas*") (EP 0416950, PTO-892).

B. Claim 7

Claim 7 stands rejected under 35 U.S.C. §103(a) in view of *Keller et al.* ("*Keller*") and *Doi et al.* ("*Doi*") (WO 98/31343), *Bjermer et al.* ("*Bjermer*") (XP-000992766) (Respiratory Medicine 91: 587-591, 1997), and *van der Molen et al. ("Molen")* (XP-000992767) (Thorax 52: 535-539, 1996).

VII. Arguments

A. Legal Standards

1. Obviousness

The Supreme Court reasserted the importance of fact-finding by the Patent Office to gather objective evidence in determining factors relevant to reaching the legal conclusion of obviousness (*KSR International Co. v. Teleflex Inc.*). The objective factors, as defined under *Graham v. John Deere Co.*, requires that the Patent Office: (1) determine the scope and content of the prior art; (2) ascertain the differences between the claimed invention and the prior art; and (3) resolve the level of ordinary skill in the pertinent art.

Furthermore, the post-KSR Examination Guidelines, currently in effect since October 10, 2007, mandates that "Once the findings of fact are articulated, Office personnel must provide an explanation to support an obviousness rejection under 35 U.S.C. 103. [The] 35 U.S.C. 132 requires that the applicant be notified of the reasons for the rejection of the claim so that he or she can decide how best to proceed.... In short, the focus when making a determination of obviousness should be on what a person of ordinary skill in the pertinent art would have known at the time of the invention, and on what such a person would have reasonably expected to have been able to do in view of that knowledge" (emphasis added) (Federal Register, Vol. 72, No. 195, p.57527, columns 2-3).

B. Secondary Considerations in Support of Nonobviousness

The Examination Guidelines confirms the necessity of including in the fact-finding process, other relevant objective evidence of nonobviousness of a claimed

invention referred to as "secondary considerations," which "may include evidence of commercial success, long-felt but unsolved needs, failure of others, and unexpected results" (emphasis added) (Federal Register, Vol. 72, No. 195, p.57527, column 2).

The Examination Guidelines states: "the key to supporting any rejection under 35 U.S.C. §103 is the clear articulation of the reason(s) why the claimed invention would have been obvious." The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. §103 should be made explicit. The Court quoting *In re Kahn* stated that "[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness."

Under MPEP § 716.01(a), such secondary considerations, including evidence of criticality or unexpected results, when present, must be considered by the Patent Office in the determination of obviousness. "A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue." *In re Corkill*, 711 F.2d 1496, 226 USPQ 1005 (Fed. Cir. 1985). Evidence of unexpected properties may be in the form of a direct or indirect comparison of the claimed invention with the closest prior art which is commensurate in scope with the claims. See *In re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980); M.P.E.P. § 716.02(b)(III).

C. Rejection of Claims 1-4, and 8 Under 35 U.S.C. §103(a) Over *Keller* in View of *Palmer Douglas*

In the final Official Action, it is alleged that *Keller* discloses an "inhalable medicinal aerosol composition comprising an effective amount of a pharmaceutically active compound selected from the group consisting of beta-mimetics ... and an effective amount of a corticoid, such as loteprednol." The Examiner has accurately noted that *Keller* "does not specifically teach the pharmaceutical composition in a powdered form," and that *Keller* "does not expressly disclose a process for the preparation of the inhalable medicinal composition in the powdered form" (emphasis added).

Furthermore, it is alleged that *Palmer Douglas's* process for making a dry powder formulation comprising classical corticosteroids and beta-mimetics can be utilized for producing the claimed powdered pharmaceutical composition comprising loteprednol or loteprednol etabonate ("soft steroid" and not the classical hard corticosteroids; these distinctions are provided in the arguments presented below) and at least one β_2 adrenoreceptor agonist.

Thus, the Examiner contends that, at the time of the invention, it would have been reasonable to expect obtaining "an inhalable composition in the powdered form by mixing well known beta-mimetics such as formoterol, salmeterol, reproterol, and corticosteroid, loteprednol because Douglas teaches [the] process for making formulations containing beta-mimetics and corticosteroids, in the powdered form for inhalation." (emphasis added) (see Official Action at pages 3-4).

Appellants respectfully disagree with the Examiner's contention that a *prima facie* case of obviousness has been established by the combined disclosures of *Keller* and *Palmer Douglas* for the following reasons.

1. *Keller's* Exemplary Formulations Do Not Disclose the Particular Combination of a Soft Corticosteroid with a β2 Adrenoreceptor Agonist as recited in Claims 1-4, and 8

Claim 1 recites: A powdered pharmaceutical composition for treating asthma bronchiale in mammals, comprising:
separately or together,
an efficacious amount of (i) loteprednol or loteprednol etabonate; and (ii) at least one β_2 adrenoreceptor agonist selected from the group consisting of salbutamol, reproterol, salmeterol, formoterol, and pharmaceutically tolerable salts there of,
for simultaneous, sequential, or separate administration by inhalation in the treatment of asthma bronchiale in mammals, wherein the pharmaceutical composition is formulated in a powdered form.

In the formulation recited in Claim 1, the (i) loteprednol functions at least as an anti-inflammatory agent, and the (ii) β_2 adrenoreceptor agonist functions at least as a bronchial dilator. Appellants assert that *Keller* and *Palmer Douglas* do not suggest the combination of the elements recited in independent Claim 1.

Claim 8 recites: A process for the preparation of a pharmaceutical composition for the treatment of asthma bronchiale, the process comprising:
combining (i) an effective amount of the active compound loteprednol or loteprednol etabonate and (ii) an effective amount of at least one β_2 adrenoceptor agonist selected from the group consisting of salbutamol, reproterol, salmeterol, formoterol, and pharmaceutically tolerable salts there of,
wherein the loteprednol or loteprednol etabonate and one or more β_2 adrenoceptor agonists are mixed individually or together,
wherein a pharmaceutically acceptable excipient or a vehicle is added if suitable, and
wherein the composition thus obtained is converted into a powdered form suitable for inhalations.

A *prima facie* case of obviousness has not been established because *Keller* and *Palmer Douglas* do not disclose the combination recited in Claim 1, and dependent Claims 2-4. First, Appellants assert that *Keller* does not disclose effective amounts of the active agents of the claimed pharmaceutical compositions, in particular, the combination of (i) loteprednol or loteprednol etabonate and (ii) β_2 adrenoreceptor agonists, contrary to the Examiner's statement. It is more factually accurate to state that *Keller* merely provides a long list of hypothetical mixtures of pharmaceutically active compounds that could be utilized as aerosol formulations in conjunction with *Keller's* method for preparing a propellant mixture comprising carbon dioxide and at least one hydrofluoroalkane having 1 to 3 carbon atoms (see *Keller*, column 5, lines 23-42). *Keller* discloses only pressure-liquefied propellant mixtures for the preparation of aerosols formulated for administration by using pressurized inhalants (see *Keller*, Table 1, column 12; Examples 1-14, columns 11-14). Thus, *Keller's* pressure-liquefied aerosol formulations are not in the same form as the powdered formulations recited in Claims 1-4.

More significantly, Appellants point out that *Keller* lists at least 34 generic classes of hypothetical agents that could be included as pressure-liquefied propellant mixtures (see *Keller*, column 7, lines 47-61; and further column 7, lines 62 -67; and column 8, lines 1-67). In particular, several examples of "beta-mimetics" are listed in column 7, lines 62-65. Examples of "corticoids" are listed in column 7, lines 66-67, and column 8, lines 1-3.

Furthermore, Appellants point out that exemplary formulations provided in *Keller* do not disclose the particular claimed composition comprising: (i) loteprednol or loteprednol etabonate and (ii) at least one β_2 adrenoreceptor agonists, as recited

in Claim 1. Example 1 provides an aerosol formulation comprising beclomethasone dipropionate (a hard corticoid) in the absence of β_2 adrenoreceptor agonists (i.e., beta-mimetics). Example 5 provides an aerosol formulation comprising budesonide (a hard corticoid) in the absence of β_2 adrenoreceptor agonists (i.e., beta-mimetics). Example 13 provides an aerosol formulation comprising beclomethasone dipropionate (a hard corticoid) in the presence of salbutamol (i.e., a type of beta-mimetics). Example 13 is the only example that suggests the combination of a hard corticoid and a β_2 adrenoreceptor agonist, however, Appellants point out that this formulation is not the equivalent of the claimed powdered formulations comprising: (i) loteprednol or loteprednol etabonate and (ii) at least one β_2 adrenoreceptor agonists, because loteprednol or loteprednol etabonate is not a hard corticosteroid. Loteprednol (or loteprednol etabonate) is not equivalent, structurally and/or functionally, to beclomethasone dipropionate, which is the species selected in *Keller's* exemplary formulation. As described adequately in the specification, loteprednol (or loteprednol etabonate) is considered to be an example of "soft corticosteroids," and in contrast, the beclomethasone dipropionate and budesonide are considered to be examples of "hard corticosteroids" (see specification at page 2, lines 23-33). Thus, Appellants submit that none of *Keller's* exemplary formulations include this particular combination of a "soft corticosteroid" (*e.g.,* loteprednol or loteprednol etabonate) with a β_2 adrenoreceptor agonist, as recited in Claim 1, comprising: (i) loteprednol or loteprednol etabonate and (ii) at least one β_2 adrenoreceptor agonists.

2. Equivalency Between Loteprednol and Keller's Exemplary Hard Steroid Compounds Has Not Been Established by Examiner; Evidence of Non Equivalency Has Been Submitted But Not Considered by Examiner

If the Examiner is assuming that hard steroids, such as beclomethasone dipropionate and budesonide, as provided in *Keller*'s exemplary formulations, are equivalent to loteprednol or loteprednol etabonate, then the Examiner has not set forth the rationale for supporting such assertions of structural and/or functional equivalency as required under the MPEP.

In the Reply filed on February 13, 2007, Appellants have distinguished the properties of soft corticosteroids (from that of classical hard corticosteroids) in the Specification by explaining that soft corticosteroids, such as loteprednols or loteprednol etabonates, are more readily metabolized (inactivated) *in vivo* by engaging a different metabolic pathway compared to classical corticosteroids, such as beclomethasone dipropionate (BDP) or budesonide (BUD), which are known to have relatively higher *in vivo* stability resulting in many deleterious side effects experienced by patients (see lines 21-31, at page 2 of the Specification). Appellants have further explained differences in the side effects produced by classical corticosteroids and soft corticosteroids to distinguish the claimed compositions and methods from the prior art (see lines 10-30, page 7 of the Specification). The claimed combination is especially beneficial for children who are especially sensitive to the deleterious side effects caused by classical hard corticosteroids, which includes growth retardation, osteoporosis, and an increase in intraocular pressure.

In the Reply filed on February 13, 2007, two technical documents were submitted in order to point out that the compounds referred to as "loteprednol" and "corticoids" (hard corticosteroids) can be structurally and functionally distinguished. Loteprednol etabonate can be structurally distinguishable from other hard corticosteroids in that the ketone group at number 20 position is not present in loteprednol etabonate that confers high lipid-solubility for enhancing penetration into cells (See "Physicians' Desk Reference: OPT - Alrex Ophthalmic Suspension 0.2% (Bausch & Lomb), at page 2 of 7, of record). In contrast to hard corticosteroids, such as beclomethasone dipropionate and budesonide, the loteprednol etabonate can be degraded in the body of patients very readily, by quickly forming inactive metabolites *in vivo* that cannot accumulate in the body at toxic levels, a characteristic of hard corticosteroids. This structural instability of loteprednol etabonate provides the desired pharmacological effect without the high toxicity inherent to hard corticosteroids, such as beclomethasone dipropionate and budesonide. In the same Reply, Appellants have submitted, as an attachment, an excerpt from Drugdex Evaluations in order to show that Loteprednol ("soft steroids") can be distinguishable from the classical hard steroids in that the two class of compounds exhibit different mechanisms of action and different levels of toxicity that results from the metabolism of these two class of steroids (see page 11 of 17). Appellants note that at the time of the present invention, loteprednol was appreciated mainly for opthalmic clinical applications, and the possibility of utilizing loteprednol etabonate in combination with beta-mimetics for the treatment of asthma bronchiale had not been appreciated.

3. Evidence of Unexpected Results and Comparative Tests

Appellants submit that the Office has not fully appreciated the experiments shown in the Specification. These experiments provide unexpected advantages, resulting from the co-administration of (1) loteprednol (or loteprednol etabonate) and (2) β_2 adrenoceptor agonists, as recited in Claim 1. The specification provides data showing synergistic effect caused by the co-exposure to a mixture of: (1) loteprednol or loteprednol etabonate; and (2) β_2 adrenoceptor agonists, under *in vitro* and *in vivo* conditions. The specification provides comparative data showing a less deleterious effect by loteprednol in comparison to classical corticosteroids. The specification also provides comparative data showing enhanced therapeutic effect by the administration of loteprednol in comparison to classical hard corticosteroids.

Table 1 of the specification shows *in vitro* synergistic (over-additive) effect (44%) of the mixture of loteprednol and salbutamol on blood cells as measured by the level of inhibition on TNF-alpha release, compared to samples exposed only to either loteprednol (1%) or salbutamol (17%) alone (see page 5 of the Specification).

Table 2 shows *in vivo* synergistic effect (36 - 65%) of a mixture of loteprednol and formoterol on guinea pigs as measured by the level of inhibition of eosinophilia, compared to samples exposed only to either loteprednol (11-22%) or formoterol (4-20%) alone (see page 6 of the Specification).

Table 3 shows gross reduction in thymus mass in rats exposed to classical corticosteroids, including fluticasone (65%), beclomethasone (51%), and budesonide (89%), in comparison to loteprednol (15-28%). This suggests that the co-administration of loteprednol in combination with β_2 adrenoceptor agonists would likely produce the over-additive effect exemplified in Tables 1 and 2 in patients, while

providing advantages for avoiding some of the deleterious side effects associated with classical hard corticosteroids (see page 8 of the Specification).

Table 4 shows enhanced therapeutic breadth after long-term exposure to loteprednol (45.5) in comparison to modest or low therapeutic efficacy observed for classical hard corticosteroids, such as fluticasone (33) and budesonide (5) (see page 10 of the Specification).

4. *Palmer Douglas* Does Not Remedy the Deficiencies of *Keller* by Disclosing Powdered Formulations of Hard Steroids in Combination with β_2 Adrenoreceptor Agonists

Because *Keller* discloses only pressure-liquefied propellant mixtures for the preparation of aerosols formulated for administration by using pressurized inhalants (see Table 1, Col. 12 of *Keller* and Examples 1-14, Cols. 11-14 of *Keller*), and does NOT disclose powdered formulations, as recited in Claims 1-4, the Examiner cites *Palmer Douglas* as providing this claim element of powdered formulation.

However, Appellants submit that *Palmer Douglas* does not remedy the deficiencies of *Keller*, in that *Palmer Douglas's* pharmaceutical compositions do not comprise (i) loteprednol or loteprednol etabonate; and (ii) β_2 adrenoreceptor agonists. *Palmer Douglas's* pharmaceutical compositions comprise a hard corticosteroid, such as beclomethasone dipropionate and budesonide in powdered form. The Examiner's reasoning appears to be that because it is feasible to make powdered formulations by combining classical hard corticosteroids with β_2 adrenoreceptor agonists, it must suggest the feasibility of producing powdered formulation of the claimed pharmaceutical composition as recited in Claim 1.

Appellants believe that if the sole purpose of *Palmer Douglas* is to demonstrate the feasibility of making powdered formulations, then any reference that describes making powdered formulations would have been sufficient. Therefore, *Palmer Douglas* does not add any substantive weight in distinguishing the subject matter of Claims 1-4 and what is disclosed in *Keller*.

The more relevant issue appears to be that *Keller* alone, or in combination with *Palmer Douglas,* fails to specifically disclose the claimed pharmaceutical composition, comprising: (i) loteprednol or loteprednol etabonate; and (ii) β_2 adrenoreceptor agonists, as recited in Claim 1. Furthermore, both of these classes of compounds, individually, have unpredictable properties, and that the efficacy of the combination of (i) loteprednol or loteprednol etabonate; and (ii) β_2 adrenoreceptor agonists was unknown until experimentally verified by the Appellants because the combined effect of these compounds was also unpredictable until reduced to practice.

Thus, Appellants assert that the cited references do not suggest the combination of the elements recited in Claim 1, and that the possibility of achieving success for this particular combination recited in Claim 1 is not reasonably expected based on the limited disclosure of the cited references. Because a *prima facie case* for obviousness has not been established, and in view of the unexpected results, Appellants respectfully request the withdrawal of the rejection of Claims 1-4 under 35 U.S.C. §103(a).

Appellants assert that a *prima facie case* for obviousness has not been established against Claim 8 directed to a method for producing the pharmaceutical composition recited in Claim 1. Thus, Appellants respectfully request the withdrawal

of the rejection of Claim 8 under 35 U.S.C. §103(a), for the same reasons set forth with respect to the rejection of Claims 1-4.

D. Rejection of Claim 7 Under 35 U.S.C. §103(a) Over *Keller* in view of *Doi, Bjermer,* and *van der Molen*

In previous and the final Official Action, the Examiner acknowledged that "*Keller* does not expressly disclose the employment of the inhalable medicinal ... composition comprising the combination as instantly claimed ...." for the treatment of asthma bronchiale. The final Official Action alleged that the requirements for a *prima facie* case of obviousness have been satisfied because: (a) *Keller* discloses "medicinal or pharmaceutical aerosol compositions comprising beta-mimetics and corticoids"; (b) *Bjermer* and *Van der Molen* "teach that β_2 agonists ... are used as inhalations in asthma treatment, and should be given in combination with corticosteroids"; and (c) *Doi* "discloses that loteprednol etabonate is known in the method of treating inflammatory conditions or allergy (asthma bronchiale ...)". Based on (a) – (c), it is alleged that persons skilled in the art would have been motivated to combine loteprednol and beta-mimetics.

Appellants disagree with the Examiner's contention that a *prima facie* case of obviousness has been established by the combined disclosures of *Keller, Doi, Bjermer,* and *van der Molen* for the following reasons.

Claim 7 recites: A method for the treatment of asthma bronchiale in a patient, the method comprising:

administering to the patient an efficacious amount of

(i) loteprednol or loteprednol etabonate and

(ii) at least one β_2 adrenoceptor agonist selected from the group consisting of salbutamol, reproterol, salmeterol, formoterol, and pharmaceutically tolerable salts there of,

wherein a pharmaceutically acceptable excipient or a vehicle is added if suitable for simultaneous, sequential or separate administration.

A *prima facie* case of obviousness has not been established because the references when combined do not disclose the method for the treatment of asthma bronchiale, as recited in Claim 7. As explained above, *Keller* does not disclose the specific pharmaceutical combination, as recited in Claim 1, nor does it suggest a method for treating asthma bronchiale, as recited in Claim 7, comprising, *inter alia*: co-administrating the combination of: (i) loteprednol or (loteprednol etabonate); and (ii) β_2 adrenoreceptor agonists as pharmaceutically effective agents.

Appellants submit that *Bjermer, Doi,* and *Molen*, do not remedy the deficiencies of *Keller* because these references when combined do not disclose/suggest the co-administration of the combination of (i) loteprednol (or loteprednol etabonate) and (ii) β_2 adrenoreceptor agonists as pharmaceutically effective agents for treating asthma bronchiale, as recited in Claim 7.

Bjermer does not disclose the specific pharmaceutical combination recited in Claims 1-4 nor does it suggest the co-administration of the combination of (i) loteprednol (or loteprednol etabonate) and (ii) β_2 adrenoreceptor agonists as pharmaceutically effective agents for treating asthma bronchiale, as recited in Claim 7. Infact, *Bjermer* discloses a mixture of (1) classical hard corticosteroids (e.g., beclomethasone dipropionate (BDP), budesonide (BUD)) and (2) β_2 adrenoceptor

agonists (e.g., bambuterol, salmeterol, and formoterol) for treating asthma (see *Bjermer,* lines 1-2 and lines 12-15 at page 588). Appellants point out that disclosing the combination of classical hard corticosteroids with a β_2 adrenoreceptor agonist is not the equivalent of disclosing the combination of a loteprednol (or loteprednol etabonate) and a β_2 adrenoceptor agonist because the classical hard corticosteroids disclosed *in Bjermer* are functionally different from the soft corticosteroids, such as loteprednol (or loteprednol), by having a different structure and a different mechanism of action compared to that of the soft corticosteroids. Thus, if one element of a claimed mixture is different from an element of a mixture taught by the cited reference, then the claimed mixture as a whole must be different from the mixture taught by the cited reference. *Molen* also discloses the combination of classical hard corticosteroids with a β_2 adrenoreceptor agonist.

Furthermore, the Examiner cites *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980, for holding that combining "two compositions, each of which is taught by the prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art" is deemed to be prima facie obvious. Applicants point out that the relevant facts have been stretched in favor to support the Examiner's conclusion of obviousness of the method of Claim 7. Of all cited references, only *Doi* describes a composition comprising loteprednol in particular, and *Doi's* composition is formulated for use as a nasal suspension, and the possibility of using the composition for the treatment of any type of asthma, let alone asthma bronchiale, in not mentioned. The Examiner states that "*Doi* discloses that loteprednol etabonate is known to be useful in a pharmaceutical composition and a

method of treating inflammatory conditions or allergy since loteprednol etabonate has excellent anti inflammatory conditions or antiallergic activities and is value as a drug in an ointment or a liquid form, and loteprednol etabonate is formuated into a long-term stable liquid suspension for nasal administration". Based on this, the Examiner alleges that "one of ordinary skill in the art could have been motivated to employ loteprednol etabonate in combination with reproterol, salmeterol, or formoterol in a method for the treatment of allergies and/or airway disorders such as asthma bronchiale" (emphasis added). If *Doi* is the only cited reference that discloses the use of loteprednol etabonate, and if *Doi* does not describe the use of the loteprednol etabonate-containing nasal drips for the treatment of "airway disorders such as asthma bronchiale," then how is the holding of *In re Kerkhoven* relevant here, when the purpose of *Doi* (anti-allergic agent) is not the same purpose as the method of Claim 7 (treatment of asthma bronchiale)?

If none of the cited references discloses or suggests the co-administration of the combination of (i) loteprednol (or loteprednol etabonate) and (ii) β_2 adrenoreceptor agonists as pharmaceutically effective agents for treating asthma bronchiale, as recited in Claim 7, then who is combining these elements? Appellants have combined the elements of Claim 7 and have experimentally tested such combinations. The Examiner bases the rejection of Claim 7 on hindsight reconstruction by asserting that the references provide "reasonable expectation of treating asthma" without establishing that there was a motivation to combine the elements of Claim 7, or establishing that the success for combining the elements of Claim 7 is reasonably expected for the treatment of asthma brochiale.

Appellants submit that absent a teaching from the cited references to combine (1) loteprednol (or loteprednol etabonate) and (2) β_2 adrenoceptor, for the treatment of asthma bronchiale as recited in Claim 7, a *prima facie case* for obviousness has not been established. Thus, Appellants assert that the cited references do not suggest the method recited in Claim 7, and that the possibility of achieving success for this method of treatment is not reasonably expected based on the limited disclosure of the cited references. Because a *prima facie case* for obviousness has not been established, and in view of the unexpected results, Appellants respectfully request the withdrawal of the rejection of Claim 7 under 35 U.S.C. §103(a).

VIII. Claims Appendix

See attached Claims Appendix for a copy of the claims at issue.

IX. Conclusion

For the foregoing reasons, reversal of the rejections of Claims 1-4, 7, and 8 is respectfully requested.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date December 27, 2007

By: _____

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VIII. CLAIMS APPENDIX

The Appealed Claims

1. (Previously Presented) A powdered pharmaceutical composition for treating asthma bronchiale in mammals, comprising:

separately or together,

an efficacious amount of (i) loteprednol or loteprednol etabonate; and (ii) at least one β_2 adrenoreceptor agonist selected from the group consisting of salbutamol, reproterol, salmeterol, formoterol, and pharmaceutically tolerable salts there of,

for simultaneous, sequential, or separate administration by inhalation in the treatment of asthma bronchiale in mammals, wherein the pharmaceutical composition is formulated in a powdered form.

2. (Previously Presented) The powdered pharmaceutical composition according to claim 1, comprising:

(i) loteprednol or loteprednol etabonate; and

(ii) formoterol.

3. (Previously Presented) The powdered pharmaceutical composition according to claim 1, comprising:

(i) loteprednol or loteprednol etabonate; and

(ii) salmeterol.

4. (Previously Presented) The powdered pharmaceutical composition according to claim 1, comprising:

(i) loteprednol or loteprednol etabonate; and

(ii) reproterol.

5. (Canceled).

6. (Canceled).

7. (Previously Presented) A method for the treatment of asthma bronchiale in a patient, the method comprising:

administering to the patient an efficacious amount of

(i) loteprednol or loteprednol etabonate and

(ii) at least one β_2 adrenoceptor agonist selected from the group consisting of salbutamol, reproterol, salmeterol, formoterol, and pharmaceutically tolerable salts there of,

wherein a pharmaceutically acceptable excipient or a vehicle is added if suitable for simultaneous, sequential or separate administration.

8. (Previously Presented) A process for the preparation of a pharmaceutical composition for the treatment of asthma bronchiale, the process comprising:

combining (i) an effective amount of the active compound loteprednol or loteprednol etabonate and (ii) an effective amount of at least one β_2 adrenoceptor agonist selected from the group consisting of salbutamol, reproterol, salmeterol, formoterol, and pharmaceutically tolerable salts there of,

wherein the loteprednol or loteprednol etabonate and one or more β_2 adrenoceptor agonists are mixed individually or together,

wherein a pharmaceutically acceptable excipient or a vehicle is added if suitable, and

wherein the composition thus obtained is converted into a powdered form suitable for inhalations.